Weighing Tumor Biology in Treatment Decisions for Patients with Non-small Cell Lung Cancer

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Abstract: Tumor molecular biology is an increasingly important consideration when choosing therapy for patients with advanced non-small cell lung cancer (NSCLC). A number of potential biological markers are under active investigation in the hope that it will be possible to identify markers that assist in patient selection for specific therapies. Distinguishing prognostic from predictive makers is crucial to the development of customized drug therapy. Some markers, such as mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR), are prognostic; patients with EGFR-mutant NSCLC have prolonged survival compared with those with wild-type disease, regardless of the treatment received. Although EGFR mutations are predictive of response to EGFR tyrosine kinase inhibitor (TKI) therapy, they do not appear to be predictive of a differential effect on survival. Other EGFR markers, such as protein expression or gene amplification, may be better predictors of a survival benefit from EGFR TKI. HER2 expression status and K-ras mutations provide additional information that may be useful in evaluating a patient for EGFR TKI therapy. Biological markers for chemosensitivity and resistance are also emerging. Patients with an elevated DNA repair capacity, evidenced by increased tumor expression of excision repair cross-complementing 1 or ribonucleotide reductase subunit M1 messenger RNA, may benefit less from cisplatin and gemcitabine, respectively, than from other agents. Increased levels of class III beta-tubulin are associated with taxane-resistance, and K-ras mutations have been associated with a lack of survival benefit from adjuvant chemotherapy in early stage NSCLC. It is likely that in the future, clinicians will evaluate a panel of biological markers in order to customize therapy for individual patients with NSCLC.

Key Words: Non-small cell lung cancer, Epidermal growth factor receptor (EGFR), Excision repair cross-complementing 1 (ERCC1), Molecular markers, Biology.

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INTRODUCTION

Despite advances in chemotherapy and the development of targeted therapies, the prognosis for most patients with advanced non-small cell lung cancer (NSCLC) remains poor. Currently, clinicians consider disease stage, patient performance status, degree of weight loss, and sex as the most important prognostic factors, and the choice of therapy is determined by the clinical picture. Significant advances are, however, being made in NSCLC tumor biology, which may ultimately lead to customized therapy based as much or more on the tumor's molecular characteristics as on the patient's clinical condition.

This review examines the prognostic and predictive markers that are currently being explored in NSCLC (Table 1). It is important to distinguish predictive and prognostic factors in this discussion. A marker is prognostic if it predicts outcome, regardless of the treatment received. A marker is predictive, however, if it predicts the outcome of a specific therapy. Before a marker can be classified as predictive and thus be used to individualize treatment, it should first be evaluated, if possible, for prognostic ability, in the absence of the treatment in question. This issue is particularly germane to the use of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), but will also be important as markers of chemosensitivity and resistance reach the clinic.

MOLECULAR MARKERS AND TARGETED THERAPY

Epidermal Growth Factor Receptor

The EGFR has emerged as an important marker in NSCLC, but considerable confusion remains regarding how to use this marker in clinical decision-making. The EGFR mutation status determined by gene sequencing, gene copy number determined by fluorescence in situ hybridization (FISH), and protein expression determined by immunohistochemistry may each contribute important information regarding which patients are likely to benefit from EGFR TKI therapy.

Evidence that EGFR mutations correlated with response to TKI therapy first emerged in 2004.[1,2] Lynch and colleagues[1] identified somatic mutations in the tyrosine kinase domain of the EGFR gene in specimens from eight out of nine patients with advanced NSCLC who had responded to gefitinib compared with none among seven patients who had not responded to gefitinib ($p < 0.001$). In-vitro analyses demonstrated that the mutations were associated with enhanced tyrosine kinase activity in response to epidermal growth factor and increased sensitivity to gefitinib. Paez and colleagues[2] also demonstrated the presence of somatic mutations in tumor samples

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TABLE 1. Biological Markers and their Potential Application in Non-small Cell Lung Cancer.

Biological Marker	Role	Potential Application
Beta tubulin	High levels associated with taxane resistance	Guide chemotherapy choice: taxane-based versus other chemotherapy
EGFR mutations	Predicts response to EGFR TKI therapy and is a prognostic marker for improved survival, independent of treatment	Identify patients likely to respond to EGFR TKI therapy
EGFR gene copy number	High gene copy number correlated with improved survival with EGFR TKI	Identify patients for EGFR TKI therapy
EGFR overexpression	EGFR protein expression correlated with improved survival with EGFR TKI	Identify patients for EGFR TKI therapy
ERCC1	Low levels correlate with prolonged survival after cisplatin/gemcitabine	Guide chemotherapy choice: platinum-based versus other chemotherapy
HER2	Increased gene copy number predicts response to gefitinib in EGFR-positive patients	Complementary to EGFR testing to identify patients with EGFR TKI therapy
K-ras	Mutation associated with lack of response to EGFR TKI therapy, but prognostic significance remains unclear	Identify patients unlikely to respond to EGFR TKI therapy
	Lack of survival benefit from adjuvant chemotherapy also reported	Identify patients unlikely to respond to adjuvant vinorelbine/cisplatin chemotherapy
RRM1	Low levels correlated with prolonged survival after cisplatin/gemcitabine	Guide chemotherapy choice: gemcitabine-based versus other chemotherapy

EGFR, Epidermal Growth Factor Receptor; TKI, tyrosine kinase inhibitor.

from NSCLC patients in the United States and Japan. They noted a correlation between EGFR mutations and patient characteristics, with mutations more common among women, non-smokers, patients from Japan, and patients with adenocarcinoma. They then evaluated the relationship between mutation status and response to gefitinib in nine patients treated with gefitinib using pretreatment tumor samples. Samples from all five of the responding patients contained EGFR kinase domain mutations, whereas none of the samples from the four non-responding patients did ($p = 0.0027$). On the basis of these data, many hypothesized that EGFR mutations would be predictive of response to EGFR TKI therapy, and that screening for these mutations may be useful to select patients for EGFR TKI treatment.

The BR.21 trial was a randomized, placebo-controlled trial of erlotinib for previously treated, advanced NSCLC. The response rate in that study was 8.9% in the erlotinib group and less than 1% in the placebo group ($p < 0.001$), and overall survival was significantly improved with erlotinib (overall survival 6.7 versus 4.7 months, respectively; $p < 0.001$). Clinical predictors of response included female sex, adenocarcinoma, Asian ethnicity, and a history of not smoking, identical to the characteristics associated with EGFR mutations in other studies. Patients with EGFR mutations had a higher response to erlotinib than did those with wild-type EGFR although the difference was not significant (15.8 versus 7.4%; $p = 0.37$).[3,4] The survival benefit from erlotinib was not, however, limited to these patients. Even though women

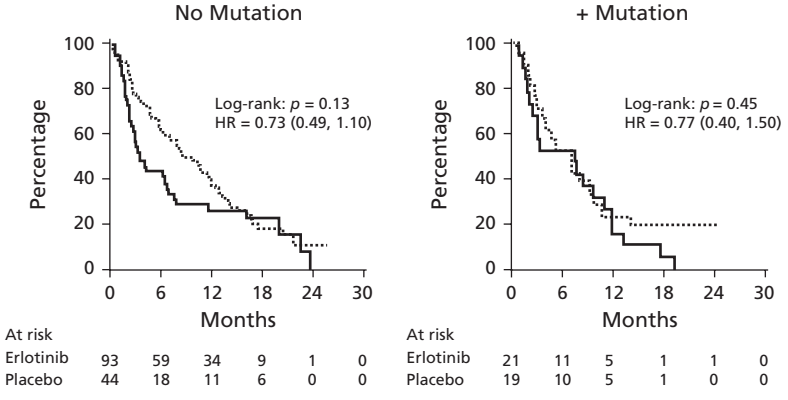

FIGURE 1. Survival According to Epidermal Growth Factor Receptor Genotype.

····· Erlotinib; —— placebo. p value for interaction 0.97.

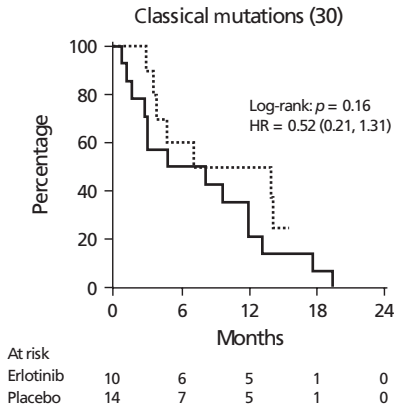

FIGURE 2. Survival for Classical Mutations (Ex19del + Ex21-l858r).

····· Erlotinib; —— placebo.

were more likely to harbor mutations, erlotinib reduced the relative risk of death by 20% in both women and men (hazard ratio [HR] 0.8 in both groups), and patients with adenocarcinoma had a similar survival benefit compared with all others. Patients with EGFR mutations also experienced a survival benefit from erlotinib, but there was no differential effect on survival based on the presence of all mutations identified (Figure 1)[4] or the presence of the classical exon 19 deletions or L858R mutations (Figure 2)[5] compared with the benefit achieved by patients who had wild-type EGFR.[4,5]

The results from BR.21 suggest that EGFR mutations are not predictive of a *differential* effect on survival in response to treatment with an EGFF TKI, although they are predictive of response, and that patients with both mutated and wild-type EGFR have the potential to benefit from such therapy. It is now becoming clear that these mutations have prognostic significance, independent of the treatment received. Sasaki and colleagues[6] evaluated the mutation status of tumors from 95 Asian patients with surgically treated NSCLC, and found that survival was significantly longer for those with tumors expressing EGFR mutations than for those with wild-type gene expression (Figure 3). Similar findings have been reported from the TRIBUTE and INTACT trials, which evaluated the addition of the EGFR TKI erlotinib and gefitinib, respectively, to first-line chemotherapy for advanced NSCLC.[7,8] Survival was significantly longer for the

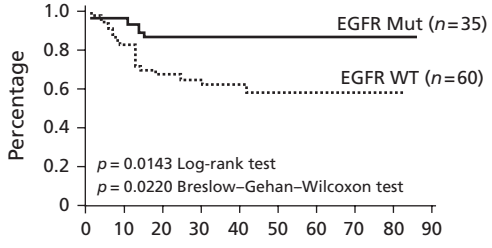

FIGURE 3. Epidermal Growth Factor Receptor (EGFR) Mutations Are Prognostic.

29 patients with EGFR-mutant tumors than for the 199 with wild-type expression in the TRIBUTE trial ($p < 0.001$) and this was independent of erlotinib therapy.[7] Erlotinib had no significant effect on survival for patients with EGFR mutations. Similarly, survival was longer for patients receiving chemotherapy alone who had EGFR-mutant disease than for those who did not in the INTACT trial (HR 0.48; 95% confidence interval [CI] 0.29–0.82).[8] Gefitinib had no significant effect on survival for patients with EGFR mutations.

Whereas the presence of EGFR mutations does not appear to predict a differential effect of EGFR TKI on survival, other EGFR tests may do so. Both EGFR protein expression and high gene copy number were associated with significantly improved survival in response to erlotinib in BR.21 when compared with placebo.[4] For patients with positive tumor EGFR protein expression, the risk of death was reduced 32% with erlotinib compared with placebo (HR 0.68; $p = 0.02$; Figure 4a).[9] Survival was not significantly improved with erlotinib for patients without EGFR expression (HR 0.93; $p = 0.7$; Figure 4b).[9] Similarly, the relative risk of death was reduced by 56% for patients with high EGFR gene copy number receiving erlotinib compared with placebo (HR 0.44; $p = 0.008$). The response rate was nearly 10 times as great for patients with a high gene copy number compared with those with a low copy number (20 versus 2.4%; $p = 0.03$), and 25% of the patients with a high gene copy number were alive at 2 years (Figure 5a and 5b).[4] The tests for interaction did not, however, reach significance for either protein expression or copy number in that study. In a similar trial (ISEL) that compared the EGFR TKI gefitinib to placebo with previously treated patients with NSCLC,[10] similar results were reported for protein expression (Figure 4c and 4d)[4] and EGFR gene copy number (Figure 5c and 5d).[9] In that trial, however, both protein expression (interaction p value 0.049) and gene copy number (interaction p value 0.045) were found to be significant predictors of a differential effect of gefitinib on survival.

Human Epidermal Growth Factor Receptor 2

HER2 is a member of the EGFR family and the preferred receptor for dimerization with EGFR upon ligand binding. Preclinical data suggest that HER2 overexpression may predict response to EGFR TKI therapy. Cappuzzo and colleagues[11] retrospectively evaluated the relationship between HER2 gene copy number and the response to gefitinib in 101 patients with NSCLC. Twenty-three (22.8%) were FISH-positive for HER2, and these patients had a significantly better response to treatment (34.8 versus 6.4%; $p = 0.001$) and time to progression (9.0 versus 2.7 months; $p = 0.02$) compared with FISH-negative patients. There was also a trend towards longer survival in the HER2-positive group (20.8 versus 8.4 months; $p = 0.056$). HER2 positivity was associated with EGFR gene expression and mutations, and patients whose tumors were positive for both markers experienced the best clinical outcomes. Conversely, those negative for

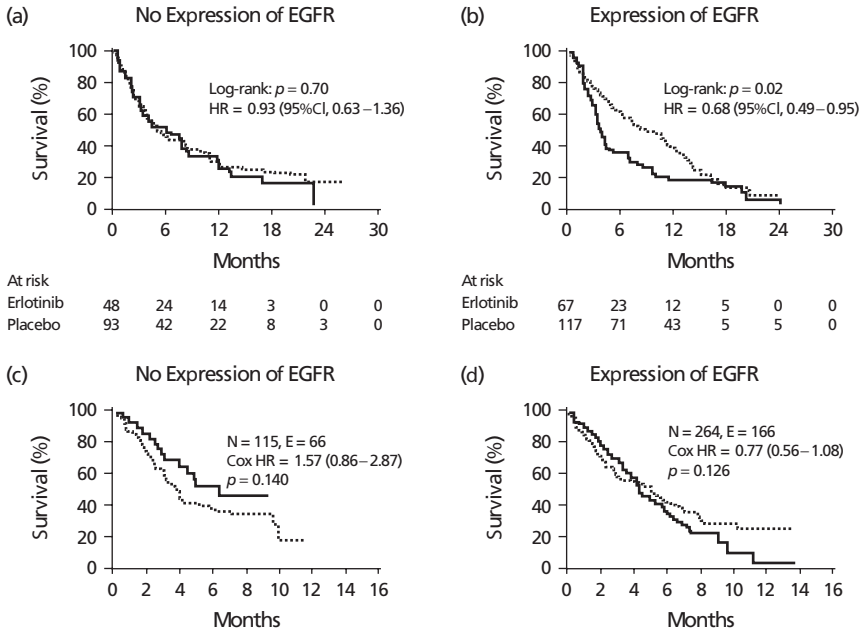

FIGURE 4. Survival by Epidermal Growth Factor Receptor (EGFR) protein expression and treatment for patients in BR.21 with no expression of EGFR (a) and with expression of EGFR (b), and for patients in ISEL with no expression of EGFR (c), and with expression if EGFR (d).[4,9]

(a) and (b) ····· Erlotinib; —— placebo; (c) and (d) ····· Gefitinib; —— placebo.

both markers experienced the worst clinical outcomes. As with the initial EGFR mutation data, it is not clear whether HER2 is a prognostic factor in NSCLC. A recent meta-analysis suggested that HER2 overexpression is associated with significantly poorer survival at 3 and 5 years, although the authors urged caution in interpretation because of the exclusion of several negative studies that lacked relevant data.[12] Nonetheless, it appears that HER2 status may add to the predictive value of EGFR expression status with respect to response to EGFR TKI therapy. It is, however, not possible to determine whether HER2 status predicts for a differential effect on survival from those studies because

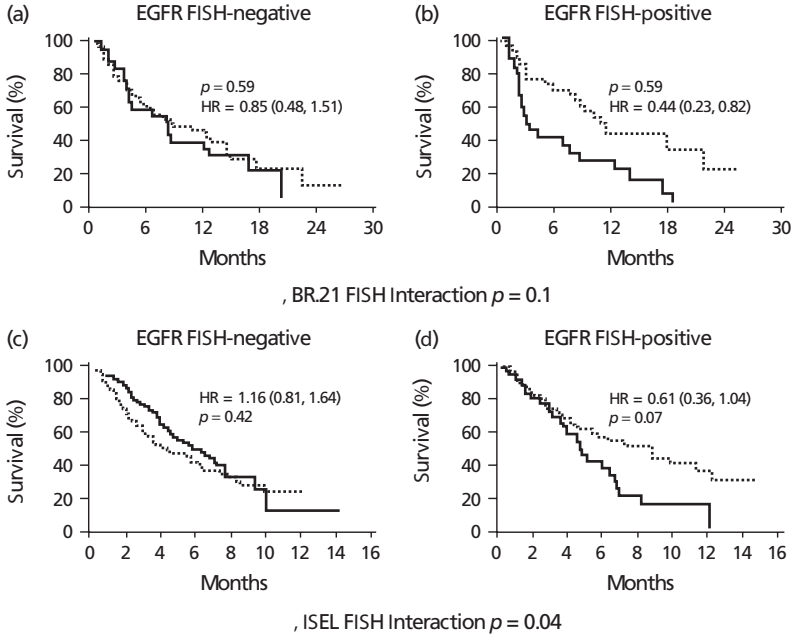

FIGURE 5. Survival by Epidermal Growth Factor Receptor (EGFR) gene copy number and treatment for patients in BR.21 with EGFR fluorescence in situ hybridization (FISH)-negative disease (a) and EGFR FISH-positive disease (b), and for patients in ISEL with EGFR FISH-negative disease (c) and EGFR FISH-positive disease (d).[4,9]

(a) and (b) ····· Erlotinib; —— placebo; (c) and (d) ····· Gefitinib; —— placebo.

all patients received treatment with an EGFR TKI and there was no placebo control arm. Furthermore, amplification of HER2 is seen rarely in patients with NSCLC (less than 10%), and so at this time, it is not possible to recommend routine testing for HER2 to select patients for EGFR inhibitor therapy.

K-ras

K-ras mutations occur in approximately 20–30% of NSCLC cases.[13] As early as 1990, data emerged suggesting that K-ras mutations are a negative prognostic marker in NSCLC. A number of studies appeared to confirm this finding; however, a similar number of studies have failed to show a negative impact on survival for patients with K-ras mutant tumors. Data are also conflicting regarding whether K-ras mutations are a predictive marker for chemoresistance in early-stage NSCLC.[14–17]

There is currently interest in exploring the relationship between K-ras mutations and EGFR. K-ras mutations and EGFR mutations appear to be functionally redundant in NSCLC because K-ras is a downstream effector of EGFR signaling. Because of this common pathway, an activating K-ras mutation could conceivably negate the effects of an EGFR TKI acting upstream. Several groups have reported that K-ras mutation is associated with a lack of sensitivity to EGFR TKI.[7,18–20] In the BR.21 trial, the K-ras genotype could be determined for 206 of the 731 patients.[20] The majority had the wild-type genotype, and 30 (15%) had a K-ras mutation. No significant difference was seen in the response to erlotinib between groups, although only one patient (5%) with mutant K-ras responded to therapy compared with 10 (10.2%) with wild-type K-ras ($p = 0.69$). Of interest is the fact that the patient with mutant K-ras who responded also had a high copy EGFR number. Patients with wild-type K-ras experienced a survival benefit that was similar to that associated with erlotinib in the primary analysis (HR 0.69; $p = 0.03$). Patients with a mutant K-ras genotype did not, however, appear to obtain a survival benefit from erlotinib (HR 1.67; $p = 0.31$). Although informative, these results should be interpreted cautiously because of the small number of patients in the analysis.

Using the data from TRIBUTE, Eberhard and colleagues[7] demonstrated that mutations in K-ras and EGFR rarely occur together. Moreover, they found that survival was significantly worse for patients with K-ras-mutant tumors who received erlotinib with chemotherapy compared with the other three patient groups. Median survival was 4.4 months for patients with K-ras mutations who received erlotinib/chemotherapy compared with 13.5 months for patients with a K-ras mutation receiving chemotherapy alone, 12.1 months for patients with wild-type K-ras receiving erlotinib/chemotherapy, and 11.3 months for patients with wild-type K-ras receiving chemotherapy alone. Given the lack of a compelling scientific explanation for these results, along with the small number of patients with K-ras mutant disease and the retrospective nature of the analyses, the finding of a negative interaction between the K-ras mutation and EGFR TKI therapy must be viewed cautiously. That said, the results are also instructive; biological markers have the potential not only to identify patients likely to benefit from certain therapies, but also those likely to be harmed by certain therapies.

MOLECULAR MARKERS AND CHEMOTHERAPY

Excision Repair Cross-Complementing 1

The cytotoxicity of cisplatin occurs mainly as a result of the formation of platinum-DNA adducts, which lead to cell cycle arrest and apoptosis. Resistance to cisplatin is related to the removal of these adducts by an innate, genetically determined DNA repair system.[21] The nucleotide excision repair system is crucial to repairing cisplatin-induced DNA damage and several major DNA repair pathways exist. The excision repair cross-complementing 1 (ERCC1) gene product is the nucleotide excision repair system enzyme responsible for recognizing platinum adducts. High tumor levels of ERCC1 messenger RNA are associated with platinum resistance in human ovarian and gastric cancer specimens.[22,23] Low levels of ERCC1 mRNA have been shown to be associated with significantly longer overall survival for NSCLC patients receiving cisplatin/gemcitabine compared with those with high levels (61.6 versus 20.4 weeks; HR 0.32; $p = 0.005$).[24] A recent retrospective analysis of data from the International Adjuvant Lung Cancer Trial (IALT), a randomized phase III trial that demonstrated a significant survival benefit for adjuvant cisplatin-based chemotherapy compared with observation in patients with completely resected NSCLC further supports the potential of ERCC1 as an important marker of platinum sensitivity.[25] In that analysis, patients with ERCC1-negative tumors who received chemotherapy had prolonged survival compared with their counterparts in the control group (HR 0.65; $p = 0.002$).[25] Conversely, survival did not differ between treatment arms for patients with ERCC1-positive tumors (HR 1.14; $p = 0.40$), suggesting that these patients were relatively resistant to the chosen chemotherapy. A standard protocol for immunohistochemical staining for ERCC1 was used for the IALT trial analysis. Although confirmation by independent studies is necessary, this immunohistochemistry protocol has the potential to be widely applicable and utilized in most pathology laboratories.

Rosell and colleagues[26] from the Spanish Lung Cancer Group conducted the first randomized trial prospectively to assess the impact of using ERCC1 protein expression levels to guide therapy. In the Genotypic International Lung Trial (GILT), patients in the experimental, or genotypic, arm were assigned to therapy based on ERCC1 mRNA tumor levels. Patients with advanced NSCLC were randomly assigned 1 : 2 to a control arm consisting of docetaxel/cisplatin or to the genotypic arm. Patients in the genotypic arm with low ERCC1 mRNA levels received docetaxel/cisplatin, whereas those with high levels received docetaxel/gemcitabine.

TABLE 2. Interim Results of GILT.[26]

	Control Arm		Genotypic Arm	
	A1 Low ERCC1 ($n = 55$)	A2 High ERCC1 ($n = 23$)	B1 Low ERCC1 ($n = 99$)	B2 High ECC1 ($n = 61$)
Overall response rate*	26 (47.3%)	6 (26.1%)	56 (56.6%)	23 (37.7%)
Complete response	4 (7.3%)	1 (4.3%)	1 (1%)	2 (3.3%)
Partial response	22 (40%)	5 (21.7%)	55 (55.6%)	21 (34.4%)
Stable disease	23 (41.8%)	13 (56.5%)	32 (32.3%)	26 (42.6%)
Progressive disease	6 (10.9%)	4 (17.4%)	11 (11.1%)	12 (19.7%)

* $p = 0.02$ (B1 versus B2 and A arms by logistic regression).

Preliminary results were reported in 2005 (Table 2). Significantly more patients in the genotypic treatment arm with low levels of ERCC1 responded to therapy than did patients in the control arm or the genotypic arm with high levels of ERCC1 ($p = 0.02$). When patients in the control arm were evaluated according to ERCC1 level, those with low levels had a better response to docetaxel/cisplatin than did those with high levels, consistent with the hypothesis that higher ERCC1 levels are associated with platinum resistance. At this first analysis, patients in the genotypic arm who had high ERCC1 levels did not respond to docetaxel/gemcitabine as well as expected. These patients tended to be older than those in the other groups ($p = 0.027$) and twice as many had squamous cell carcinoma (43 versus approximately 20% in the other groups; $p = 0.009$). In the final analysis, the objective response rate in the combined genotypic arm was 50.7%, which was significantly greater than the 39.3% response rate ultimately seen in the control arm ($p = 0.024$). This improvement in response did not, however, translate into a significant improvement in survival.

Ribonucleotide Reductase Subunit M1

Ribonucleotide reductase subunit M1 (RRM1) is another potential biomarker for predicting response to chemotherapy, particularly gemcitabine. Ribonucleotide reduction is essential to DNA synthesis. Ribonucleotide reductase converts ribonucleotide 5′-diphosphate to deoxyribonucleotide 5′-diphosphate, whereas gemcitabine competes with ribonucleotide 5′-diphosphate for incorporation into DNA. The overexpression of ribonucleotide reductase would be expected to interfere with the efficacy of gemcitabine, and preclinical studies have supported this hypothesis. The overexpression of ribonucleotide reductase has been observed in gemcitabine-resistant oropharyngeal, leukemia, and NSCLC cell lines.[27–29] Moreover, in lung cancer cell lines that were modified to over or underexpress RRM1, sensitivity to gemcitabine was highest when RRM1 expression was low and resistance was seen when RRM1 expression was high.[30]

Clinical trial data support these preclinical observations. The Spanish Lung Cancer Group reported that among patients with advanced NSCLC who were treated with gemcitabine/cisplatin, median survival was significantly longer for those whose tumors had low expression levels of RRM1 mRNA compared with those with high expression levels (13.7 versus 3.6 months, $p = 0.0009$).[31] The expression of RRM1 mRNA was strongly correlated with ERCC1 mRNA expression ($p < 0.001$). Bepler and colleagues[30] at the H. Lee Moffitt Cancer Center also demonstrated that RRM1 expression is predictive of response to gemcitabine. They found that RRM1 expression was significantly inversely correlated with the magnitude of disease response in 30 patients with locally advanced NSCLC who received induction chemotherapy with gemcitabine and carboplatin. They also recently completed accrual to a phase II clinical trial that assigns patients with advanced NSCLC to therapy based on biomarker expression levels.[32] Patients with low ERCC1 expression received platinum-based therapy: carboplatin/docetaxel for those who also had high RRM1 expression or carboplatin/gemcitabine for low RRM1 expression. Patients with high ERCC1 expression received docetaxel-based therapy: docetaxel/vinorelbine for high RRM1 expression or docetaxel/gemcitabine for low RRM1 expression. Outcomes of interest included response rates and progression-free and overall survival.

Beta-Tubulin

The taxanes exert antitumor activity by interfering with microtubule dynamics. By binding to beta-tubulin, one of the major components of microtubules, the taxanes ultimately produce growth arrest at the G2-M phase of the cell cycle. Beta-tubulin occurs in at least six distinct isotypes in humans, and the overexpression of a particular isotype, class III beta-tubulin, is emerging as a mechanism behind taxane resistance.[33] High levels of class III beta-tubulin expression are associated with taxane resistance in human cancer cell lines, including lung, ovarian, prostate, breast, and pancreatic cancer.[34–37] High levels of expression have been associated with clinical resistance to taxane therapy in breast and ovarian cancer patients.[38,39] Similar results were not seen, however, in a trial of postoperative adjuvant vinorelbine and cisplatin, suggesting that this marker may be more useful in predicting response to taxanes than to the vinca alkaloids, which also target the microtubule.[40]

To explore further the potential of class III beta-tubulin as a prognostic or predictive marker in NSCLC, Seve and

TABLE 3. Outcomes for Patients with Advanced and Early-Stage Non-small Cell Lung Cancer Receiving Chemotherapy by Class III Beta Tubulin Tumor Expression Levels.

Advanced Non-small Cell Lung Cancer

	Taxane-treated		Gemcitabine-treated	
	Low Beta Tubulin ($n = 22$)	**High Beta Tubulin ($n = 25$)**	**Low Beta Tubulin ($n = 17$)**	**High Beta Tubulin ($n = 27$)**
Response rate, %	62	13*	33	33
Progression-free survival, days	335	105†	165	140
Overall survival, days	525	206‡	334	223

Early-Stage Non-small Cell Lung Cancer

	Vinorelbine-treated		Observation	
	Low Beta Tubulin ($n = 72$)	**High Beta Tubulin ($n = 68$)**	**Low Beta Tubulin ($n = 60$)**	**High Beta Tubulin ($n = 65$)**
Recurrence-free survival, years	Not reached	Not reached‡	Not reached	1.5
Overall survival, years	Not reached	7.8	Not reached	4.3

* $p < 0.001$;
† $p = 0.004$;
‡ $p = 0.002$.

colleagues[33] conducted a retrospective study with data from patients treated with taxane-based or gemcitabine-based chemotherapy for advanced NSCLC. Taxane therapy consisted of paclitaxel with either cisplatin or carboplatin. Patients in the gemcitabine-treated group received either gemcitabine alone or in combination with cisplatin or carboplatin. Among the 45 evaluable paclitaxel-treated patients, the response rate was 37.5%. All clinical outcomes were significantly better for paclitaxel-treated patients whose tumors expressed low levels of class III beta tubulin (Table 3).[33,40] The response rate was five times higher for patients with low expression, and survival was more than twice as long, compared with the paclitaxel-treated patients with high expression levels. Conversely, no such differences were seen among the gemcitabine-treated patients when compared by class III beta tubulin tumor expression levels. These findings provide strong evidence that the overexpression of class III tumor expression by NSCLC tumor cells has predictive value for paclitaxel therapy, but is not itself a prognostic factor.

Seve et al.[40] also conducted a sub-analysis of the JBR.10 trial to determine the impact of class III beta tubulin on patient outcomes and benefit from adjuvant cisplatin/vinorelbine. In contrast to the findings in advanced disease that response rates are higher in patients with low tubulin expression, findings showed that high class III beta tubulin expression was associated with a greater survival benefit from adjuvant chemotherapy (Table 3). The reason for this discrepancy is not yet known. Similar to findings in advanced disease, high class III beta tubulin expression was associated with poor prognosis in surgery-only patients. Remaining questions include whether patients with low tubulin expression derive benefit from adjuvant cisplatin/vinorelbine and whether tubulin status is associated with benefit from other adjuvant regimens. Accordingly, tubulin status cannot yet be used for patient selection or adjuvant treatments.

In conclusion, the use of tumor molecular markers holds great promise for customizing therapy and providing optimal treatment to individual patients. There are currently a number of effective regimens available for the management of patients with advanced NSCLC. In the absence of specific biological tests to guide the choice of treatment, many patients are prescribed therapy for which the likelihood of benefit is unknown. Using clinical characteristics such as sex or ethnicity may improve the likelihood of response to EGFR TKI therapy, but it may also erroneously deny the therapy to patients without the typical characteristics who could benefit from such treatment. Moreover, not all patients chosen for EGFR TKI therapy based on favorable clinical characteristics will experience prolonged survival with treatment; chemotherapy may be a better choice for certain patients. It is likely that a panel of tests will be used in the future to determine not only which patients are likely to respond to EGFR TKI therapy, but which patients are likely to experience prolonged survival with such treatment.

Tumor molecular biology may also potentially play a role in selecting chemotherapy regimens for individual patients. Markers have been identified that predict response to platinum-based therapy, taxane-based therapy, and gemcitabine, and clinical trials are underway to determine whether chemotherapy customization based on these markers improves outcomes. In the future, oncologists will work closely with colleagues in pathology to evaluate each patient's tumor molecular profile and determine an appropriate, customized treatment plan. It is hoped that such customized therapy finally may lead to significant survival gains in this challenging disease.

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